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Progress in the testing of surfactant-stabilized neutral insulin (Hoe 21 PH) in various dispensing systems
Grau, U.

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To increase insulin stability in implantable pumps Hoe 21 PH, a neutral insulin prepn. stabilized against denaturation on hydrophobic surfaces by ***Genapol*** , was examd. In vitro tests indicated an improvement in performance under peristaltic pump conditions while maintaining quality and stability of Hoe 21 PH.
Genapol insulin stabilized

PROGRESS IN THE TESTING OF SURFACTANT STABILIZED NEUTRAL INSULIN (HOE 21 PH) IN VARIOUS DISPENSING SYSTEMS

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Introduction

The relative instability of insulin in a dosing system environment is a well established fact (1,2). The most difficult problem is the tendency of insulin to denaturation with the concomitant appearance of insoluble precipitates and disappearance of biological potency. This process is highly dependent on contact materials, on temperature, on mechanical action, and on time. Thus, to obviate denaturation external pumps utilizing regular insulin are to be refilled about every other day and catheters and the complete drug pathway are to be discarded at the same time. Nevertheless, this laborious and costly procedure is the routine insulin pump treatment nowadays, which is, moreover, restricted to subcutaneous access.

Surfactant stabilized insulin Hoe 21 PH has been developed initially with the prime focus on implantable insulin dosing devices. However, here some data on the use of Hoe 21 PH in the external H-tron infusor will be presented along with long term results in implantable pumps.

Characteristics of Hoe 21 PH

Hoe 21 PH is a buffered, neutral, isotonic, and phenol-preserved insulin preparation stabilized against denaturation on hydrophobic surfaces by the addition of 10 ppm of polyethylene-polypropyleneglycol (Genapol TM) (2,3). The properties and a proposed mechanism of stabilization have been published. In brief, genapol prevents the strong adsorption of insulin to hydrophobic surfaces by altering their physical-chemical character (Figure 1).

Compatibility of Hoe 21 PH and the H-tron infusor

The H-tron infusor is a small, lightweight and easy-to-use, yet versatile, external insulin pump equipped with a glass syringe holding a ca. 7-day insulin supply. The performance of the pump and Hoe 21 PH have been tested at 37° C, constant shaking, at very low dispensing rates (0.36 ml/day) in 4 subsequent refill cycles of 8, 10, 9 and 9 days. To aggravate the test conditions, the same reservoir and catheter have been used repeatedly.

The quality and quantity of delivered insulin as it leaves the catheter tip have been analyzed using high performance liquid chromatography (HPLC). Quantity was determined with reference to an external standard, while quality was expressed as percentage of individual insulin and derivative

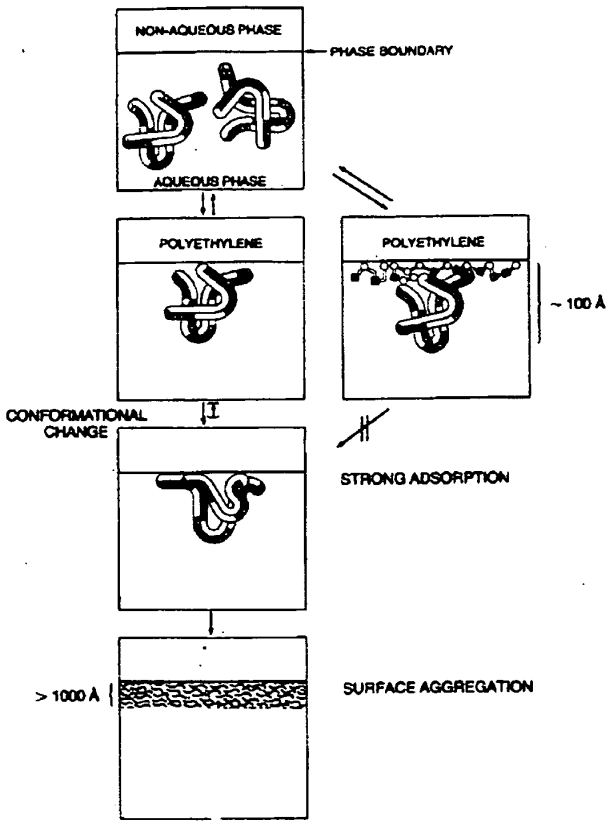

Figure 1:

Sketch of insulin adsorption onto hydrophobic surfaces and its prevention by a surface active stabilizer (right panel)

peaks of the total insulin amount. The HPLC conditions and further experimental details have been published (4). The results (Figure 2) show that the insulin amount is always near 100%, as is the percentage of native, unmodified insulin. The major modification product and insulin dimers account for typically less than 2% of the total insulin. This excellent result does not differ significantly from reference samples stored in glass vials at 37°C (the usual storage of insulin is between 2°C and 8°C).

Subsequent to the in vitro test, the drug pathway has been analyzed using scanning electron microscopy and Xray microanalysis. Potential insulin deposits can be detected by the sulfur signal, since insulin contains six cysteins. The teflon-catheter turned out to be remarkably smooth and clean along its entire length. Only near the tip we detected at two points microscopic deposits at 6000 fold magnification. These very likely could be trace contaminations caused by the insulin solution upon sample preparation.

Compatibility of Hoe 21 PH and the Pacesetter implantable programmable infusion pump (IPIP)

The Pacesetter IPIP is a sophisticated, almost all-titanium, pulsatile pump (5) which has proven to be highly compatible with Hoe 21 PH both in vitro and in vivo. These tests have now been extended from 4-week refill cycles to refills

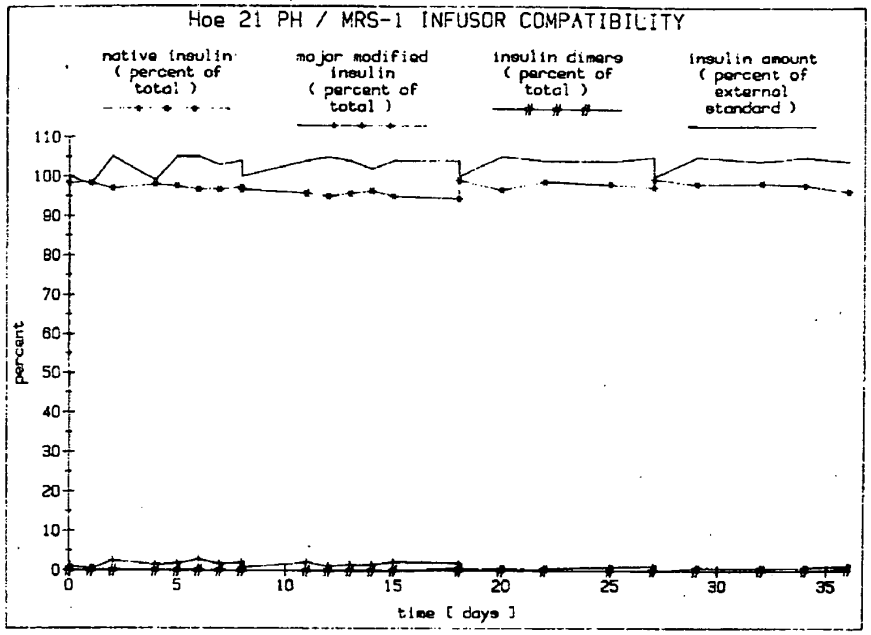

Figure 2: HPLC results of the compatibility tests of Hoe 21 PH and the H-tron MRS-I infusor

of 35, 54, and 71 days, while decreasing the rate to 60 µl/day. The environmental conditions have been maintained at 37 C and constant shaking. The results of one such experiment are shown in figure 3. Initially, the device had been filled with a placebo solution and no flushing was performed; it took about 20 days until the insulin reached the catheter tip in near expected quantity (note that dilution by 1:1.2 had occurred due to the dead volume of the reservoir). Between days 70 and 90 the insulin quantity was increased because accidentally slight evaporation had occurred in the collecting vial. Otherwise, the insulin leaving the catheter was always present in near original amount, no signs of turbidity were apparent. Moreover, the insulin quality was always near the quality of the original solution charged into the reservoir. Insulin dimers and major modification products were below 3%. The tests of Hoe 21 PH and IPIP are still in progress.

Thus, an implanted insulin pump holding an insulin supply per refill for about 3 months is a feasability for diabetes therapy.

Compatibility of Hoe 21 PH and other implantable pumps

Several implantable insulin pumps are under development (5), the simplest being the gas driven bellows constant basal rate Infusaid pump. Again, this pump is fabricated from carefully selected materials and is highly compatible with Hoe 21 PH based on in vitro studies. On the other hand, peri-

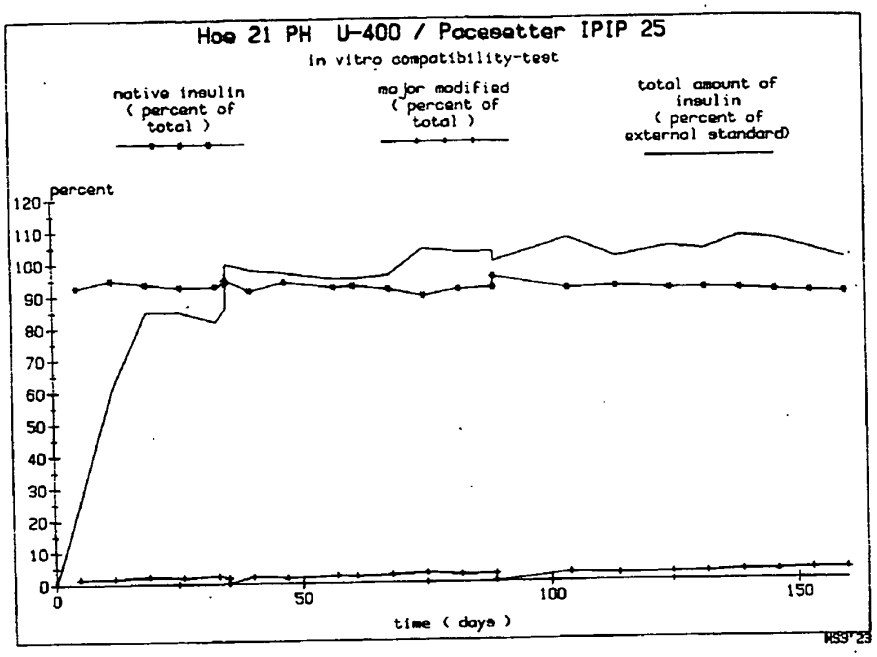

Figure 3: HPLC results of the compatibility tests of Hoe 21 PH U-400 and the Pacesetter IPIP

staltic pumps (e.g. the Siemens and Medtronic pumps) are most elegant and versatile from a technical point of view, yet the stress on insulin within the elastomer tube is much more severe. The mechanism of insulin denaturation in peristaltic pumps is not entirely understood; however, strong insulin adsorption (figure 1) does take place on the silicon elastomer despite the presence of the stabilizer (2).

The testing of Hoe 21 PH with the Siemens pump under extreme in vitro conditions has sometimes yielded insulin precipitates after about 3-6 months. However, results in dogs were far better because 1) the in vivo system is a closed system not suffering from evaporation problems, for instance, 2) the dog is not constantly moving 3) total insulin delivery is higher and 4) insulin delivery includes boluses.

Recently, one Siemens device has been implanted in a human in Munich; this pump has been functioning well for more than a year with Hoe 21 PH on ca. 10 day refill cycles. Insulin quality and quantity in the reservoir have been satisfactory always (Figure 4), and metabolic control has been good (6).

In an effort to even further increase insulin longterm stability in a peristaltic pump environment, a new insulin preparation of elevated viscosity (Hoe 21 GH) has been examined. Various in vitro tests indicate a substantial improvement in performance under peristaltic pump conditions, while maintaining the superior quality of Hoe 21 PH regarding general stability.

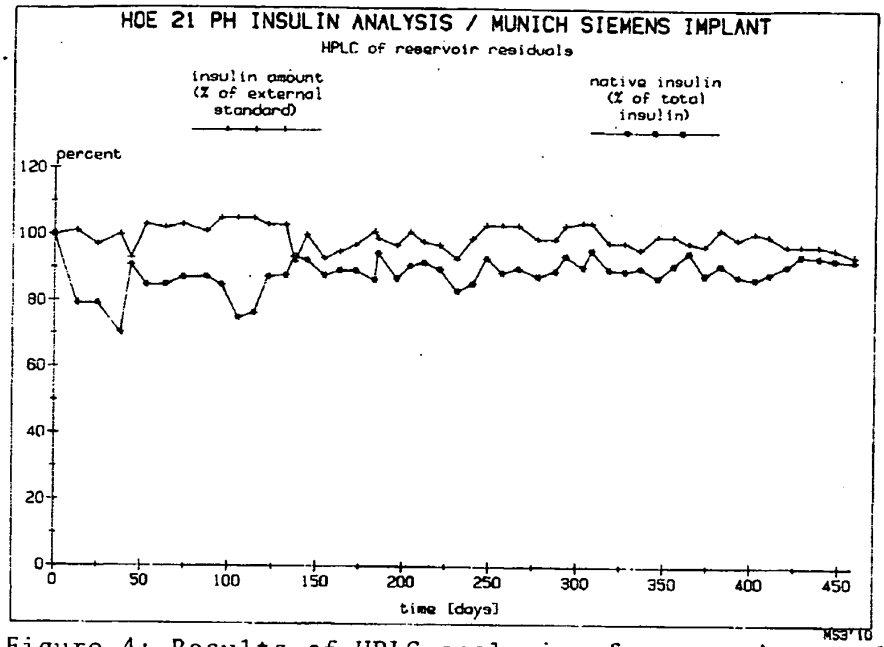

Figure 4: Results of HPLC analysis of reservoir samples from the Siemens pump implanted in a human

References

1. Irsigler, K. & Kritz, H. (1979) Long-term continuous intravenous insulin therapy with a portable insulin dosage-regulating apparatus. Diabetes, 28, 196-203.
2. Grau, U. (1985) Insulin stability. In Continuous Insulin Infusion Therapy (Eds) Hepp, K.D. & Renner, R. pp. 33-46. Stuttgart - New York: Schattauer.
3. Thurow, H. & Geisen, K. (1984) Stabilization of dissolved proteins against denaturation at hydrophobic interfaces. Diabetologia, 27, 212-218.
4. Grau, U. (1985) Chemical stability of insulin in a delivery system environment. Diabetologia, 28, in press.
5. Taylor, G., Lebisch, H. et al. (1983) Devices and Materials. Reports from representatives of industry. In Diabetes Treatment With Implantable Insulin Infusion Systems (Eds) Irsigler, K., Kritz, H. et al., pp. 29-39, Munich - Vienna - Baltimore: Urban & Schwarzenberg.
6. Walter, H., Bachmann, W. et al. (1985) Implantation of a programmable insulin infusion device in a type I diabetic patient with subcutaneous insulin resistance. Abstr. XII Congress of the I.D.F., Madrid, Sept. 23.-28.